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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 09/485,292      | 05/03/2000  | ULRICH KLAR          | SCH1742             | 1743             |

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EXAMINER

CHANG, CELIA C

ART UNIT PAPER NUMBER

1625

DATE MAILED: 09/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 09/485,292             | KLAR ET AL.         |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Celia Chang            | 1625                |  |

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08/04/06.
- 2a) ☒ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,5,6,8-12,31 and 32 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,6,8-12,31 and 32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)             | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### DETAILED ACTION

1. Applicants filed an after final remark requesting that the finality of the office action be made non-final because claim 32 was in the previous amendment.

Therefore, the finality of the previous office action has been withdrawn and the after final remark has been considered a response to the non-final action dated April 28, 2006.

A restriction and election was made dated Jun 12, 2002 and the scope of examination was clearly delineated in the office action dated Aug. 27, 2002 to be:

“Claims 1-30 drawn to the compounds of formula I where D-E is CH<sub>2</sub>CH<sub>2</sub>, X is CR<sub>10</sub>R<sub>11</sub>, where R<sub>10</sub> is 4-thiazolyl substituted with alkyl or 4-oxazole substituted with alkyl, R<sub>11</sub> is H, C<sub>1</sub>-20 alkyl, R<sub>1a</sub> and R<sub>1b</sub> are independently H, C<sub>1</sub>-10 alkyl, carbocyclic aryl, C<sub>7</sub>-C<sub>20</sub> aryl, R<sub>6</sub> and R<sub>7</sub> taken together forms a bond or are each H, R<sub>8</sub> is H, C<sub>1</sub>-C<sub>20</sub> alkyl, carbocyclic aryl, C<sub>7</sub>-C<sub>20</sub> carbocyclic aryl which can be optionally substituted with nonheterocyclic rings, Y is O, Z is O, the process of producing a compound of formula I as defined above”

With respect to the above restriction and the scope of examination, no traverse was made (see response Mar. 4, 2003). Thus, this restriction was made final dated May 27, 2003.

Subsequent office actions and RCE have been examined and based on this scope of election and examination.

Applicants are reminded that the scope of examination is continuous of the above scope. The insertion of the R<sub>10</sub> or R<sub>11</sub> moieties with non-elected invention would be an impermissible switch. Therefore, the scope of examination is continuous of the above scope and the other contemplated non-elected scope will stay withdrawn.

Claims 3-4, 7, 13-30 have been canceled. Claims 1-2, 5-6, 8-12, 31-32 are pending.

Attorney argued that it was improper for the examiner to restrict since initially the office presented an election of species and should follow the election of species procedure. Attorney's attention is drawn to that in the response to the election of species attorney elected the species corresponding to the first compound of claim 8 (i.e., (4S, 7R, 8S, 9S, 13Z, 16S (E))-4,8-dihydroxy-7-ethyl- 16-( 1 -methyl-2-(2-methyl-4-thiazolyl) ethenyl)- 1 -oxa- 5,5,9,13-tetramethyl-cyclohexadec- 13-ene-2,6-dione (A) and commented that the election of species procedure should follow unless unity of invention was lacking. The office on Aug. 27, 2002 clearly have made it clear in the record, a “restriction” was made because *unity of invention was lacking*. The lack of unity not only was clearly stated in the Aug. 27, 2002 office action, it is clearly of

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record that such lacking of unity was found in the international search/examination report (see reports submitted Feb. 8, 2000 with translation). Attorney made no traversal for the restriction and there is no good reason after six office action that attorneys now demand that a restriction was improper and should follow the election of species procedure. An election of species was clearly corrected after finding the inventions lacking unity as of record in the PCT reports and such correction was clearly delineated in the Aug. 27, 2002 office action. Attorneys had ample opportunity to traverse the restriction before it was made final.

Claims 1-2, 5-6, 8-12, 31-32 are continuously examined for the above elected scope and the other contemplated non-elected scope will stay withdrawn, cancellation is recommended.

2. The rejection of claims 1-2, 5-6, 9-12 and 31 under 35 USC 112 first paragraph as failing to comply with the written description requirement is maintained for reason of record.

As clearly delineated in the previous office action, a survey of the specification evidenced that there is no description of the instantly amended scope wherein "one of R<sup>10</sup> or R<sup>11</sup> is H and the other is 2-methyl-4-thiazolyl". Compounds containing 2-methyl-4-thiazolyl has been exemplified but no generic "description" to such invention was found in the specification. Please note that the definition for the generic formula did not contain 2-methyl-4-thiazolyl moiety (see page 4 and entire description for formula I). Applicants argument that the specification provides a structure and reference to naturally occurring epothilone A and B which does not obviate the lack of antecedent basis for the instantly amended scope of claims 1-2, 5-6, 9-12 and 31. Please note that while examples and derivatives to the naturally occurring epothilone can be claimed as independent species as such compounds being made and described in the specification, such examples do not offer any support for a "subgeneric scope" for which no description or antecedent basis was found in the specification.

The court has clearly set forth that Markush claims should be noted that this type of claim is employed when there is no common accepted generic expression which is commensurate in scope with the field which the applicants desires to cover (see Ex parte Ohsumi 21 USPQ2d 1020) and Markush group is a listing of specific alternatives of a group in a patent claims which is a sort of homemade generic expression covering a group of two or more different material (see Abbot v. Baxter 67 USPQ2d 1191). In other words, Markush elements are artificial elements

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put together in a claim, if the “alternative” such as 2-methyl-4-thiazolyl, has not be explicitly named in the Markush grouping, it is not included. While the compounds containing 2-methyl-4-thiazolyl can be claimed as independent compounds, no antecedent basis for a Markush group containing 2-methyl-4-thiazolyl can be found.

The new matter rejection based on newly created genus is proper and maintained for reason of record.

Attorneys argued that “...the examiner is *trying* to get applicants to narrow their invention to a more limited subgenus by calling an election of species requirement a Restriction” is completely misplaced. As it was clearly found from the prosecution history that the “lacking of unity” was clearly of record from the PCT international examination authority as well as the instant office, thus, a corrective “restriction” was issued on Aug. 27, 2002.

Please note that even if the election of species was followed, the international search report found 14 “X” references, then, the search would be limited to the elected species in view of such enormous number of anticipatory/obvious references.

In view of the lacking of unity, and the no common accepted generic expression which is commensurate in scope with the field which applicants desire to cover, found by the instant national stage prosecution and the international search authority, the lacking of descriptive support and the issue of new matter is clear of record.

3. The rejection under the judicially created doctrine of obviousness type double patenting over allowed claims 1-5, 17-18, 20-21 or 10/631,011 are maintained for reason of record.

Please note that a terminal disclaimer not only disclaimed the terminal portion of the issued claims but also binds the patents with obvious variations together so that multiple legal action will not be imposed to the public. As it was clearly delineated that the allowed claims in view of the issued patent US 6,610,736 rendered the instant claims *prima facie* obvious, a terminal disclaimer against the earliest patent and binding all the allowed claims together should be filed. Please note that the conjugate of 10/631,011 are prodrugs of the instantly claimed hydroxyl compounds. Prodrug conjugates are *prima facie* obvious formulation of compounds for delivery purposes.

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Attorneys argued that the two sets of claims do not encompass "same subject matter". Please note that the rejection is not on structural similarity but on "prodrug" being prima facie. Please note that the 6,610,736 provided support for the broadened scope of 10/631,011 when R8 is more than the instant R8 to include the halogen and cyano of the issued '736 claims.

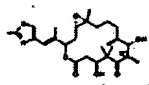
Since no terminal disclaimer was filed, the rejection is maintained.

4. The rejection of claims 1-2, 5-6, 9-12 and 31 under 35 USC 103(a) over CA 132:293587 is maintained for reason of record.

Applicants argument with respect to the Declaration is very confusing. In the first place, it is noted that none of the tested compounds provided in the 132 Declaration has the D-E being CH<sub>2</sub>CH<sub>2</sub> linker while the proviso of the instant claims are limited to R<sup>2a</sup> and R<sup>2b</sup>. It is meaningless to compare the R<sup>2a</sup> and R<sup>2b</sup> is methyl compound to the ethyl compound because with D-E being the instant claimed linker, R<sup>2a</sup> and R<sup>2b</sup> being methyl or ethyl are all included. It is very confusing as to what are the attorney arguing about since the relationship between the instant generic claims and the prior art compounds are genus and species relationship, there is no evidence why the species guided by the generic teaching of the prior art would not render the instant genus containing all the species of the prior art obvious (see CA 132 exemplified D-E being epoxy, CH=CH etc.).

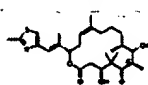
Applicants argued that all compounds of the 132 Declaration have the CH<sub>2</sub>CH<sub>2</sub> linker is erroneous. The 21 compounds presented by the declaration either have the

DE is epoxy



or

DE is CH=CH



None of the compounds has DE=CH<sub>2</sub>CH<sub>2</sub>. Regardless of how close the comparative structures are, none of the comparison is commensurate with the election or the examined scope.

5. The following rejection was considered new ground and thus the previous office action is now made non-final.

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 8 and 32 being drawn to the 2-methyl4-thiazolyl compounds (please note the other heterocyclic moieties such as pyridinyl are non-elected and stayed withdrawn) are rejected under 35 U.S.C. 103(a) as being unpatentable over Danishefsky et al. US 6,242,469.

Determination of the scope and content of the prior art (MPEP §2141.01)

Danishefsky et al. has a 102(e) provisional filing date of Dec. 3, 1996. A species wherein D-E is CH<sub>2</sub>CH<sub>2</sub> Y is O, R<sup>2a</sup> and R<sup>2b</sup> are H and methyl compound (see Fig. 42B, compound 34 with anti-leukemia activity).

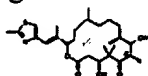
Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Danishefsky et al. generically disclosed that R<sup>2a</sup> and R<sup>2b</sup> substituents are optionally linear or branched chain alkyl (see col. 6, line 65-66).

Finding of prima facie obviousness—rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would be in possession of the instantly claimed compound since such compounds are generically described by Danishefsky et al. and a specific example with potency would guide one skill in the art to prepare and use any and all of the compounds of the generic scope with the expectation of having similar activity. In absence of unexpected results, there is nothing unexpected in choosing some among many. In re Lemin 141 USPQ 814.

Please note that for the elected scope D-E is CH<sub>2</sub>CH<sub>2</sub>, a saturated ring must be found as following:



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Attorneys are urged to compare all the structure on the 132 Declaration wherein all of them have DE being CH=CH or DE=epoxide. None of the compounds is within the instantly elected subject matter wherein D-E is CH<sub>2</sub>CH<sub>2</sub>.

All the above rejections have been made in the April 29, 2006 office action which has now been made non-final. Attorney's argument has also been fully addressed.

**6. THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

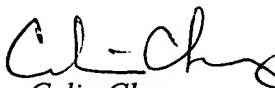
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

**7.** Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang  
April 27, 2006

  
Celia Chang  
Primary Examiner  
Art Unit 1625